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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/374,586	08/13/1999	DAVID J. PINSKY	59167/JPW/JM	3944

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JOHN P WHITE
COOPER & DUNHAM LLP
1185 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/07/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/374,586	Applicant(s) David J. Pinsky
	Examiner First Last	Art Unit 1234

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 29, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-13, 16-20, 22-24, and 27* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-13, 16-20, 22-24, and 27* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment filed 7-29-02 has been entered. Claims 21, 25 and 26 have been canceled. Claims 2, 4, 8 and 17 have been amended. Claim 27 has been added. Claims 1-13, 16-20, 22-24 and 27 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "which polypeptide comprises consecutive amino acids having the sequence shown in SEQ ID No. 1" in claim 27 is vague and renders the claim indefinite. It is unclear what polypeptide is being referred to: the deletion mutant, substitution mutant, insertion mutant, or CD39 polypeptide.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

> make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 17-20 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 17-20 and 22-24 are directed to a method for determining whether a compound which increases ADP catabolism inhibits platelet aggregation or leucocyte accumulation and does not increase intracerebral hemorrhage (ICH) for treating or preventing thrombotic or ischemic disorder in a subject by using an animal model and measuring the stroke outcome and the incidence of ICH, and comparing the stroke outcome and incidence of ICH with or without a test compound. The method of determining whether a compound does not increase ICH by measuring the incidence of ICH and comparing the incidence of ICH with or without the test compound is considered new matter because the specification fails to provide support for such method. Page 14 lines 19-32 of the specification cited in the amendment filed 7-29-02 only discloses measuring stroke outcome, platelet and/or fibrin deposition and comparing the results but fails to support the claimed method set forth above.

5. Claims 1-13, 16 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of soluble CD39 in the treatment and prevention of thrombotic and ischemic disorders in mice and BIBU52 in rhesus and marmoset monkeys

(Guth et al., abstract), does not reasonably provide enablement for the use of CD39 polypeptide for treating or preventing stroke in a human subject, or for the use of an active fragment comprising amino acid 1-50 of SEQ ID No. 2 or about 20-80 amino acid of SEQ ID No. 1 that mimics the active site, or for the use of any deletion mutant, insertion mutant, or any truncated mutant of CD39 polypeptide for treating or preventing stroke in a human subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-13, 16 and 27 are directed to a method for treating or preventing stroke in a human subject comprising administering to the human subject a CD39 polypeptide comprising SEQ ID No. 1 or an active polypeptide fragment thereof, an active fragment comprising amino acid 1-50 of SEQ ID No. 2 or about 20-80 amino acid of SEQ ID No. 1 that mimics the active site, or a deletion mutant, insertion mutant, or a truncated mutant of CD39 polypeptide to inhibit ADP-mediated platelet aggregation by increasing ADP catabolism without increasing incidence of ICH in the human subject.

The claims encompass using a CD39 polypeptide, any active fragment comprising amino acid 1-50 of SEQ ID No. 2 or about 20-80 amino acid of SEQ ID No. 1 that mimics the active site, or any deletion mutant, insertion mutant, or any truncated mutant of CD39 polypeptide to treat or prevent stroke in a human subject. The specification only discloses the use of soluble CD39 in the treatment and prevention of thrombotic and ischemic disorders in mice. Guth

discloses a nonpeptidic molecule, BIBU52, that can inhibit the aggregation of human platelets in platelet-rich plasma induced by collagen, ADP, and a thrombin-receptor activating peptide. BIBU52 inhibits aggregation in plasma from rhesus and marmoset monkeys but not in rat plasma (e.g. abstract).

The specification fails to provide adequate guidance and evidence whether and how a CD39 polypeptide comprising the sequence of SEQ ID No. 1 or active fragment thereof, or active fragment comprising amino acid 1-50 of SEQ ID No. 2 or about 20-80 amino acid of SEQ ID No. 1 that mimics the active site, any deletion mutant, insertion mutant, or any truncated mutant of CD39 polypeptide can be used to treat or prevent stroke in a **human subject** and **does not increase incidence of ICH**.

Gura (Science, Vol. 278, p. 1041-1042, 1997) reports "The fundamental problem in drug discovery for cancer is that the (animal) model systems are not predictive at all" and "The animals apparently do not handle the drugs exactly the way the human body does. And attempts to use human cells in culture don't seem to be faring any better, partly because cell culture provides no information about whether a drug will make it to the tumor site" (e.g. p. 1041, first column). Similarly, the effect of a CD39 polypeptide comprising SEQ ID No. 1 or its active fragment thereof in treating or preventing stroke in mouse model does not necessarily mean that said CD39 polypeptide or its active fragment thereof could be used to treat or prevent stroke in a human subject and does not increase incidence of ICH. The specification and the teachings of the prior art only disclose the effect of CD39 polypeptide in vitro or in mouse model. There is no

evidence of record that a CD39 polypeptide comprising the sequence of SEQ ID No. 1 or active fragment thereof, or active fragment comprising amino acid 1-50 of SEQ ID No. 2 or about 20-80 amino acid of SEQ ID No. 1 any deletion mutant, insertion mutant, or any truncated mutant of CD39 polypeptide can be used to treat or prevent stroke in a **human subject** and **does not increase incidence of ICH**. The claims specify treating or preventing stroke in a human subject but the specification fails to provide sufficient enabling disclosure to enable the claimed method. One can not extrapolate the therapeutic effect in an animal model, such as a mouse model, to the success in treating or preventing stroke in a human subject. Therefore, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed.

In addition, the specification fails to provide adequate guidance and evidence whether and how an active fragment comprising amino acid 1-50 of SEQ ID No. 2 or about 20-80 amino acid of SEQ ID No. 1 that mimics the active site (claims 6 and 7), any deletion mutant, insertion mutant, or any truncated mutant of CD39 polypeptide (claim 27) can be used to treat or prevent stroke in a **human subject** and **does not increase incidence of ICH**. The specification only discloses using a soluble CD39 polypeptide in treating or preventing stroke in mice and the cited reference, i.e. Schulte et al., 1999, discloses that apyrase conserved regions (ACR)-1, -4, and -5 within CD39 polypeptide are required for maintenance of biochemical activity of the CD39 polypeptide (e.g. abstract). Therefore, a Cd39 polypeptide mutant must comprise ACR-1, -4, and -5 in order to maintain its biochemical activity so as to treat or prevent stroke in mice. The

claims encompass using any CD39 polypeptide mutant comprising only one or two ACRs to treat or prevent stroke in a **human subject** and **does not increase incidence of ICH**. There is no evidence of record that any CD39 polypeptide mutant comprising only one or two ACRs can be used to treat or prevent stroke in a **human subject** and **does not increase incidence of ICH**. There is also no evidence of record that adding additional amino acid residues between ACRs within CD39 polypeptide would not affect the biochemical activity of the CD39 polypeptide for treating or preventing stroke in a human subject and does not increase incidence of ICH.

Further, The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional

sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). In view of the lack of evidence that a CD39 polypeptide or its various mutants can be used to treat or prevent stroke in a human subject and does not increase incidence of ICH and the unpredictability of a protein function from mere amino acid sequence, one skilled in the art at the time of the invention would not know how to use the claimed CD39 and its variants for the claimed method.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples given and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.